J. Dairy Sci. 100:1–13
https://doi.org/10.3168/jds.2016-11679

Estimating genetic and phenotypic parameters of cellular immune-associated traits in dairy cows

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ABSTRACT

Data collected from an experimental Holstein-Friesian research herd were used to determine genetic and phenotypic parameters of innate and adaptive cellular immune-associated traits. Relationships between immune-associated traits and production, health, and fertility traits were also investigated. Repeated blood leukocyte records were analyzed in 546 cows for 9 cellular immune-associated traits, including percent T cell subsets, B cells, NK cells, and granulocytes. Variance components were estimated by univariate analysis. Heritability estimates were obtained for all 9 traits, the highest of which were observed in the T cell subsets percent $CD4^+$, percent $CD8^+$, $CD4^+$:$CD8^+$ ratio, and percent $NKp46^+$ cells (0.46, 0.41, 0.43 and 0.42, respectively), with between-individual variation accounting for 59 to 81% of total phenotypic variance. Associations between immune-associated traits and production, health, and fertility traits were investigated with bivariate analyses. Strong genetic correlations were observed between percent $NKp46^+$ and stillbirth rate (0.61), and lameness episodes and percent $CD8^+$ (−0.51). Regarding production traits, the strongest relationships were between $CD4^+$:$CD8^+$ ratio and weight phenotypes (−0.52 for live weight; −0.51 for empty body weight). Associations between feed conversion traits and immune-associated traits were also observed. Our results provide evidence that cellular immune-associated traits are heritable and repeatable, and the noticeable variation between animals would permit selection for altered trait values, particularly in the case of the T cell subsets. The associations we observed between immune-associated, health, fertility, and production traits suggest that genetic selection for cellular immune-associated traits could provide a useful tool in improving animal health, fitness, and fertility.

Key words: dairy cow, immune-associated trait, heritability, variance

INTRODUCTION

Dairy cow health represents a major constraint on production and is a significant cause of poor welfare. This is particularly true in the case of the modern high-yielding dairy cow, where periods such as early lactation carry a heightened risk of disease and susceptibility to mastitis and other mammary infections is increased (Collard et al., 2000; McDougall et al., 2007). Genetic selection for increased milk yield has been highly successful; however, it has also resulted in unforeseen negative effects on health, longevity, and production (Pryce et al., 2004; Oltenacu and Broom, 2010; Koeck et al., 2013; Pritchard et al., 2013). The ability to predict the occurrence of disease in dairy cows is crucial in maintaining a high level of production within a herd as well as ensuring any financial loss is kept to a minimum (Huijps et al., 2008). Two examples of approaches to improve dairy cow health are to identify phenotypic markers (i.e., biomarkers) that can be used to predict the occurrence of health events and allow early intervention, or to identify heritable traits associated with improved health function for use in future genetic-selection programs aimed at reducing disease incidences and health conditions. Recently, interest has been growing in identifying and measuring immune-associated (**IA**) phenotypes in livestock, which could then be associated with disease or health conditions. Such IA phenotypes could be used to estimate an individual's susceptibility to disease or act as biomarkers of concurrent disease (Park et al., 2004; Clapperton et al., 2005, 2008, 2009; Flori et al., 2011a,b; Thompson-Crispi et al., 2012a,b; van Knegsel et al., 2012; Banos et al., 2013). Previous research has looked at either steady-state measurements, such as circulating leukocyte populations, acute phase proteins, and serum cytokine levels (Park et al., 2004; Glass et al., 2005; Clapperton et al., 2005, 2008; Flori et al., 2011a,b; Banos et al., 2013), or in

Received June 29, 2016.
Accepted December 8, 2016.
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vitro measurements of immune responsiveness focusing on innate and adaptive arms of the immune response (Thompson-Crispi et al., 2012a,b, 2014b; Heriazon et al., 2013; Mallard et al., 2015). Moreover, it has been suggested that including measurable immune response phenotypes in selection indices may be a viable option to decrease disease and improve animal health (Abdel-Azim et al., 2005; Thompson-Crispi et al., 2012a; Mallard et al., 2015)

Previously, using a cohort of 248 lactating Holstein-Friesian dairy cows sampled repeatedly over a 10-mo period, we identified several cellular IA traits within the circulating leukocyte population that were significantly associated with important health, fertility, and lactation traits, including mastitis, lameness, and infertility. These included a negative association between the $CD4^+$:$CD8^+$ T lymphocyte ratio and subclinical mastitis, a negative association between percent $CD8^+$ T lymphocytes within the total circulating leukocyte population and fertility, and a positive association between percent $NKp46^+$ leukocytes and lameness. Furthermore, these cellular measures were highly repeatable and displayed significant between-animal variation, suggesting they may be altered by genetic selection (Banos et al., 2013).

The aim of the present study was to add to the previous findings by using a larger data set, and corresponding pedigree information, to estimate genetic and phenotypic variance components for various subsets of blood leukocytes. Further, we investigated the genetic and phenotypic associations between these cellular IA traits and health, fertility, production, and functional traits (e.g., SCC, feed intake, live weight, BCS) in dairy cows.

MATERIALS AND METHODS

Animals

All animals in the study population were Holstein-Friesians from the Langhill lines of dairy cattle housed at the Scotland's Rural College Dairy Cattle Research Centre at Crichton Royal Farm, Dumfries, Scotland. Cows were born between January 2003 and September 2012 and were between their 1st and 5th lactation (inclusive). Cows in the Langhill herd are routinely and extensively monitored for productivity, health, welfare, and reproduction, generating a wealth of phenotypic data for use in statistical analyses. Full pedigree spanning 7 generations was available.

Langhill cows are involved in an on-going selection experiment in a 2 by 2 approach (genetic line × feeding systems) that has been running for over 30 yr (Veerkamp et al., 1994). Cows are divided equally between 2 genetic groups: a control and a select. Those in the control group were daughters of sires selected with the UK-average genetic merit for milk fat and protein. In contrast, cows in the select group were from sires selected with the highest genetic merit for milk fat and protein (Pryce et al., 1999; Bell et al., 2011). Within each genetic group, cows were also divided among 2 distinct feed groups that aimed to be divergent in terms of energy content. From 2002 to 2009 animals were split between an indoor nongrazing, low-forage system with a target ME of 12.3 MJ/kg of DM, with the other half of the herd receiving a high-forage diet with summer grazing with a target ME of 11.5 MJ/kg of DM. From September 2009 cows moved to different diets, either a home-grown forage diet (home-grown) or a bought-in by-product feed (by-product). Over summer, the animals on the home-grown forage diet were at grass during the day and overnight they were offered a feed of appropriate home-grown ingredients to balance the high protein and relatively low NDF of the grass. The by-product diet was based on ingredients available following a primary production process and not normally used for human food (March et al., 2016).

Data

Detailed animal performance data were collected on the cows routinely while they were on the genetic line × feeding systems. The present study included 546 cows with IA trait information. Of these, 256 were previously included in Banos et al., (2013). An additional 246 cohorts without IA trait information were also available and included in the bivariate analyses, resulting in a total of 792 cows with yield, reproductive, and health measures. The data are summarized in Table 1 and described in further detail below.

IA Traits. Blood samples were collected on 12 separate occasions from 358 animals (2,266 total samples).

Table 1. Description of phenotype data set used in all model analyses

Description	Total
Weekly production and functional phenotypic records	92,153
Weekly cellular immune-associated, health, and fertility records	3,581
Animals in data set	792
Animals with immune data	546
Animals with phenotypic data only	246
Lactations	3[1]
Years (2005–2015)	10
Animals in pedigree	2,793
Sires	539
Dams	1,813
Generations	7

[1]1,785 total lactations. Note: lactations ≥3 are grouped into the lactation 3 class.